IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:
Martin Ashdown

Serial No.: 10/576,981

Filed: March 2, 2007

Atty. Docket No.: 5517-18

For: Method Of Therapy

Group Art Unit: 1648

Examiner: Bo Peng

Conf. No.: 8112

DECLARATION OF
DR. BRENDON J. COVENTRY
UNDER 35 U.S.C. § 132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Brendon J. Coventry, do hereby declare as follows:

1. My curriculum vitae and a biography are provided. My employment and educational history are summarized also. I have significant experience in the treatment of cancer using a variety of techniques and therefore, possess at least a level of ordinary skill in the art.

2. I am familiar with the above-identified patent application. I am aware that claims of the application are directed to a method for analyzing immune system cycling to determine when an agent should be administered to a patient suffering from cancer. Conventional therapies for treatment of cancer include: chemotherapy, radiation therapy, and surgery. The intended mode of action for such conventional therapies is to either kill (e.g., by chemotherapy or radiotherapy) or remove (e.g., by surgery) cancer cells. The complete response rates from clinical trials with anti-cancer drugs has remained remarkably low and consistent for different cancer types, suggesting the existence of a common underlying mechanism or factor relevant to all cancers and treatments.

3. The invention claimed in the present application is a dramatic change in approach for the treatment of cancer, in other words, a paradigm shift from existing treatment concepts. In an article in Bioshares entitled *Are We Ready for the World's Biggest Paradigm Shift in Cancer Therapy?*, I am quoted as saying "A cure for cancer is not about killing dividing cancer cells the way we have been thinking about it in the past, but appears to be the way immune cells are being killed, depending on the timing of the administration of our therapies." Conventional therapies have focused on killing cancer cells, whereas this invention is focused on killing certain immune cells by understanding the dynamics of persistent immune system cycling within a patient.

4. I am aware that Claims 45-47, 49-50, 58, 59, 61 and 62 have been rejected as being obvious over WO 2003/068257 (WO '257) in view of Huber (Huber et al., Cancer Res., 40:3484-90, 1980).

5. I have read WO '257 and am familiar with the description and references presented in that patent publication.

a. The inventors of WO'257 teach a means by which to take advantage of the phenomenon of the beneficial administration of agents when suppressor cells begin to become active by "resetting" the immune system by, for example, reducing the tumor load so that there is some tumor antigen-based stimulation of effector cells and then immediately looking for emerging effector and regulator T cell populations to treat the patient, such that effector cell activity is predominately maintained, while reducing or minimizing regulator cell activity.

b. As is clear from WO'257, the window between resetting the immune system and administration of an agent is relatively narrow, such as about two weeks following the "resetting" event. For instance, Example 1 of WO'257 shows a dramatic difference between administration of an agent at 14 days vs. 15 days following resetting.

c. By modifying WO'257 as suggested by the Examiner to arrive at the claimed invention, a skilled person would be acting contrary to the teaching of WO'257, which requires resetting the immune system, such as by reducing tumor load, and then treating the patient as soon as suppressor cells begin to become more active. In contrast, the present invention requires that a patient is monitored for at least one cycle of the immune system without resetting.

d. The present invention is significantly distinct from the resetting invention of WO'257 because WO'257 requires a resetting step, whereas the present invention does not, and the present invention requires monitoring a patient for at least one cycle of the immune system, whereas WO'257 does not.

6. In the Office Action mailed December 1, 2009, the Patent Office states that Huber, in the Abstract and on p. 41 ***[sic]***, teaches cycling of the immune system between periods of cytotoxic and suppressor cell activity; and in the Office Action mailed June 3, 2010, the Patent Office states that Huber (at pp. 3485 and 3489) suggests there is a continued cycling of cytolytic and suppressive immune cells in immune responses in animals. The Office further states that while Huber does not actually show continued cycling beyond a first cytolytic phase, a first suppressive phase, and an additional cytolytic phase; this appears to be due to the death of the animals being monitored, rather than an indication that the cycling terminates after these three phases.

7. I have read Huber in connection with preparation of this declaration, but was not previously aware of it. I am familiar with the data presented in Huber and the author's discussion of that data. I believe that data in Huber do not support the position of the Patent Office, described above in Paragraph 6, that is, that Huber suggests persistent cycling.

a. The Patent Office states that the lack of a showing of persistent cycling in Huber is due to early animal deaths. However, the fourth and fifth graphs of Chart 1 in Huber show rats surviving to 24 and 32 days without showing additional cycling occurring from day 16 onward. Further cycling should have been seen in the time period from day 16 to either day 24 (fourth graph) or day 32 (fifth graph). The reason Huber did not show persistent cycling (perhaps insufficient sampling or sampling at the wrong times) is not clear, but at least in the fourth and fifth graphs of Chart 1, the rats survived long enough that cycling should have occurred. The fact that Huber did not show persistent cycling in those graphs would preclude concluding that Huber suggests to a skilled person that persistent cycling of the immune system occurs.

b. The early and late phase cytotoxic lymphocytes in Huber were inhibited differently by suppressor cells (Huber, pages 3487-88), suggesting that these two phases are not the same, and in agreement with the author's description of these effects as separate phases.

From this result, a skilled person would infer that these two phases are not recurring as part of any persistent cycle.

8. A number of researchers over the years have studied the immune response to tumors. These are principally using implanted tumours in animal models. Robert J. North has published in this area and several of his publications are being submitted in this application. For example, in North and Bursuker (1984), Fig. 10 is a diagrammatic representation of the immune response to a progressive immunogenic tumor of the type represented by the meth-A fibrosarcoma. This figure suggests just a single peak of effector cells in response to the tumor and not cycling of effector cells.

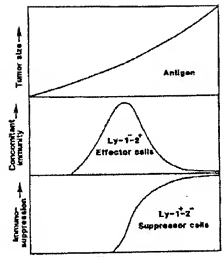

FIGURE 10. Diagrammatic representation of the immune response to a progressive immunogenic tumor of the type represented by the meth A fibrosarcoma. After the tumor reaches a critical minimum size it provides enough antigen to evoke the generation of Ly-1$^-$2$^+$ effector T cells. However, a short period of additional tumor growth provides antigenic conditions that favor the generation of Ly-1$^+$2$^-$ suppressor T cells that function to down-regulate the production of Ly-1$^-$2$^+$ effector T cells. Consequently, not enough effector T cells are made to destroy the tumor.

9. The poster attached as Exhibit A, "Individualized (Timed) Delivery of Standard Chemotherapy as a means of immune reconstitution in patients with metastatic melanoma", Quevedo et al., Poster presented at 2009 ASCO Annual Meeting, provides evidence that practice

of the presently claimed invention provides superior results compared to conventional cancer therapy. This study was conducted by the inventor Martin Ashdown with researchers from the Mayo Clinic (Rochester, MN) and the University of Melbourne (Melbourne, AU).

a. This poster describes the results of a clinical pilot study of 12 patients with metastatic melanoma in which C-reactive protein (CRP) levels were measured. All of the patients exhibited oscillating CRP levels. (See graph marked A) One of the patients was not treated because of rapid tumor progression.

b. Of the remaining patients, nine had tumor progression in less than five months. These patients were treated by chemotherapy with temozolomide in the post-peak section of the CRP cycle. This section of the CRP cycle corresponds to a time in the immune system cycling when regulator cell numbers and/or activity are not increasing in the cycle, that is, not in accordance with the claims of the present invention.

c. The two remaining patients remained progression free for more than two years and had been treated by chemotherapy with temozolomide in the pre-peak section of the CRP cycle. This section of the CRP cycle corresponds to a time in the immune system cycling when regulator cell numbers and/or activity are increasing in the cycle, as is claimed.

10. I hereby declare that all statements made herein to my own knowledge are true and that all statements made on information are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent.

12/5/11
Date

Brendon S. Coventry

Curriculum Vitae - Brendon J. Coventry

Qualifications:-	Bachelor of Medicine
	Bachelor of Surgery
	Doctor of Philosophy (Immunology)
Professional Membership:-	Fellow of the Royal Australasian College of Surgeons
Current Posts:-	Assoc. Professor of Surgery, Adelaide University
	Director of the Cancer Immunology Laboratory and Immunotherapy Program, Discipline of Surgery, University of Adelaide
	Senior Consultant Surgeon, Royal Adelaide Hospital

Professor Brendon Coventry, BMBS, FRACS, PhD is Associate Professor of Surgery at the University of Adelaide, and is Foundation Director of the Adelaide Melanoma Unit, Royal Adelaide Hospital. He also holds appointments as Chair, Surgical Oncology Section, Royal Australasian College of Surgeons; and Immediate Past Chair, Melanoma and Skin Cancer Section, Clinical Oncological Society of Australia; Foundation Member and South Australian Representative, Australian and New Zealand Melanoma Trials Group; and is Clinical Investigator for National Cancer Institute, National Institutes of Health, USA. He is an active clinical surgeon, performing general surgery, surgical oncology and trauma surgery. Dr Coventry holds several teaching and academic posts in Medicine and Surgery, and has an excellent research record with publications in over 60 peer-reviewed publications and 30 conference presentations. He has contributed to 8 book chapters, including as a co-author for 4th and 5th Editions of Charles Balch's 'Cutaneous Melanoma', and is Chief Editor of an international text 'Surgical Risks, Complications and Consequences' of over 1400 pages with 80 international contributors. He has a notable track record in securing competitive grants that fund collaborative research both locally and internationally. Some clinical research projects in melanoma include: role as Principal Investigator running two NIH International Multicentre Polyvalent (C-VAX) Melanoma Vaccine trials for Stage III & IV metastatic melanoma, in collaboration with the John Wayne Cancer Institute, CA, USA and CancerVax Corporation; Heat-Shock Protein Melanoma Vaccine trial for advanced metastatic melanoma in collaboration with Antigenics Corporation, Boston, USA; Vaccinia Melanoma Cell Lysate Vaccine trial for treatment of advanced Stage IV melanoma with and without chemotherapy in collaboration with Professor Peter Hersey (University of Newcastle, NSW); and Principal Investigator in a Multicentre National Collaborative Melanoma Peptide Vaccine Trial for the treatment of advanced melanoma (in collaboration with Prof Hersey, Newcastle and Sydney Melanoma Units). He is also a PI in the NIH sponsored International Multicenter Selective Lymphadenectomy Trial in collaboration with Professors Don Morton and Alistair Cochran at the John Wayne Cancer Institute and UCLA, CA, USA. He holds a PhD in Immunology, which focussed on the immunology and immunotherapy of solid tumours, and has continued laboratory investigations of dendritic cell and T-cell expression and function in human melanoma and breast cancer. His recent translational research work has been into clinical vaccine therapies and the role of dendritic cells, regulatory T-cells in patient immune responses and the critical importance of timed vaccine and chemotherapy. He is a Senior Examiner for the Australian Medical Council and University of Adelaide.